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Comparison of three methods for the synthesis of carborane carboxylic acid esters

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Abstract

Three procedures for the esterification of polyhedral carborane carboxylic acids with long chain unsaturated fatty alcohols are compared with regard to rate of reaction, ease of isolation and over-all yield. The optimum procedure is based on room temperature reaction of the acid chloride and alcohol in the presence of 4-dimethylaminopyridine in CH_2Cl_2.

Graphical Abstract

Esterification of 1,2-dicarbaclosododecaboranyl monocarboxylic acid with ten unsaturated fatty alcohols, as exemplified here with palmitoleyl alcohol, occurs most efficiently *via* reaction of the acid chloride and alcohol in the presence of p-dimethylamino pyridine.

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Regular Article

Unsaturated Long-Chain *N*-Acyl-vanillyl-amides (N-AVAMs): Vanilloid Receptor Ligands That Inhibit Anandamide-Facilitated Transport and Bind to CB1 Cannabinoid Receptors*[1]

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Abstract

We investigated the effect of changing the length and degree of unsaturation of the fatty acyl chain of *N*-(3-methoxy-4-hydroxy)-benzyl-*cis*-9-octadecenoamide (olvanil), a ligand of vanilloid receptors, on its capability to: (i) inhibit anandamide-facilitated transport into cells and enzymatic hydrolysis, (ii) bind to CB1 and CB2 cannabinoid receptors, and (iii) activate the VR1 vanilloid receptor. Potent inhibition of [^{14}C]anandamide accumulation into cells was achieved with C20:4 n-6, C18:3 n-6 and n-3, and C18:2 n-6 *N*-acyl-vanillyl-amides (N-AVAMs). The saturated analogues and Δ^9-*trans*-olvanil were inactive. Activity in CB1 binding assays increased when increasing the number of *cis*-double bonds in a n-6 fatty acyl chain and, in saturated N-AVAMs, was not greatly sensitive to decreasing the

chain length. The C20:4 n-6 analogue (arvanil) was a potent inhibitor of anandamide accumulation (IC_{50} = 3.6 μM) and was 4-fold more potent than anandamide on CB1 receptors (Ki = 0.25–0.52 μM), whereas the C18:3 n-3 N-AVAM was more selective than arvanil for the uptake (IC_{50} = 8.0 μM) vs CB1 receptors (Ki = 3.4 μM). None of the compounds efficiently inhibited [^{14}C]anandamide hydrolysis or bound to CB2 receptors. All N-AVAMs activated the cation currents coupled to VR1 receptors overexpressed in *Xenopus* oocytes. In a simple, intact cell model of both vanilloid- and anandamide-like activity, i.e., the inhibition of human breast cancer cell (HBCC) proliferation, arvanil was shown to behave as a "hybrid" activator of cannabinoid and vanilloid receptors.

Author Keywords: cannabinoid; endocannabinoid; capsaicin; analgesics; breast cancer cells; carrier

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*1 Abbreviations used: N-AVAM, *N*-acyl-vanillyl-amide; VR1, vanilloid receptor type 1; RBL, rat basophilic laukemia; CB1, CB2, cannabinoid receptor type 1 and 2; TRP, transient receptor potential; TRPL, transient receptor potential-like; RTX, resiniferatoxin; FAAH, fatty acid amide hydroxylase; AM404, *N*-(4-hydroxyphenyl)-arachidonylamide; anandamide, *N*-arachidonoyl-ethanolamine; olvanil, *N*-(3-methoxy-4-hydroxy)-benzyl-*cis*-9-octadecenoamide; palvanil, *N*-(3-methoxy-4-hydroxy)-benzyl-hexadecanamide; arvanil, *N*-(3-methoxy-4-hydroxy)-benzyl-arachidonylamide; pseudocapsaicin, *N*-(3-methoxy-4-hydroxy)-benzyl-nonanamide; HBCC, human breast cancer cell

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